Yearly Prostate Specific Antigen and Digital Rectal Examination Fluctuations in a Screened Population

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Purpose: Prostate biopsy is often recommended based on increases in prostate specific antigen and/or abnormal digital rectal examination. We investigated the stability of a single positive test during the next 3 consecutive years.

Materials and Methods: A total of 2,578 participants in a San Antonio screening cohort with 2 or more consecutive annual prostate specific antigen and digital rectal examination tests were identified. Occurrences of an increased prostate specific antigen (2.5 ng/ml or greater) followed by 1 or more nonincreased prostate specific antigen results were compared with similar fluctuations of digital rectal examination from abnormal to normal.

Results: In 2,272 men who did not have a biopsy during the study, in 23.3% of 744 incidences of an increased prostate specific antigen with 1 year of followup, the next prostate specific antigen was not increased. In 19.5% of 462 incidences of an increased prostate specific antigen with 2 years of followup, the next 2 consecutive prostate specific antigen levels were not increased. Finally, in 17.5% of 285 incidences of an increased prostate specific antigen with 3 years of followup, the next 3 consecutive prostate specific antigens were not increased. Rates were similar but lower in 221 men with 1 or more negative biopsies during the study and in 85 men in whom prostate cancer eventually developed during the study. In contrast, approximately 70% of abnormal digital rectal examinations were normal the following year even in patients with prostate cancer, and in the majority of incidences remained normal the next 2 to 3 consecutive years.

Conclusions: Occurrences of reversed prostate specific antigen cut point or abnormal digital rectal examination based decisions to biopsy 1 or more years after the initial test are not uncommon, suggesting repetition of these tests.

Key Words: prostate-specific antigen, digital rectal examination, time factors

Abbreviations and Acronyms

DRE = digital rectal examination

PSA = prostate specific antigen

SABOR = San Antonio Center of Biomarkers of Risk for Prostate Cancer

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PROSTATE specific antigen in serum and digital rectal examination are the most commonly used tools for screening for prostate cancer.[1] The widespread use of PSA and DRE have resulted in a dramatic increase in prostate cancer detection in the last decade.[2] While the rate of detection of organ confined disease has increased with subsequent improvement in curability, there has been an undisputed increase in the detection of clinically insignificant cancers subjected to unnecessary treatment and related morbidity.[3] The use of PSA and DRE for screening in prostate cancer detection has been a subject of relentless debate.[4] Outcomes regarding potential

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benefits of screening will not be known until the results of the ongoing Prostate, Lung, Colorectal and Ovarian Cancer trial in the United States and the European Randomized Study of Screening for Prostate Cancer in Europe are reported.[5,6] Both screening tests have been used in a dichotomous manner in clinical practice. Patients are generally advised to undergo prostate biopsy if PSA exceeds a cutoff of 2.5 or 4.0 ng/ml, or if DRE is abnormal. Recent reports have suggested caution while recommending prostate biopsy based on a single increased PSA.[7] While natural biological variation occurs in PSA testing in the short term, year-to-year fluctuations in serum PSA have also been reported in unscreened populations.[7,8] Transrectal ultrasound guided biopsy of the prostate, although technically simple, is an invasive procedure that may lead to significant bleeding and infection related complications.[9] In this study we evaluated the year-to-year changes in serum PSA and DRE findings in a prospectively studied cohort based on biopsy recommendations and biopsy findings.

MATERIALS AND METHODS

The San Antonio Center of Biomarkers of Risk for Prostate Cancer is a Clinical and Epidemiological Validation Center of the Early Detection Research Network of the National Cancer Institute. Since 2000 SABOR has recruited 3,651 men without a diagnosis of prostate cancer into a longitudinal followup study. Participants have been followed annually by their SABOR affiliated clinician with DRE and PSA measurement. The SABOR clinicians are credentialed to perform DRE and are approved by the institutional review board to perform it. They perform the DRE blinded to the PSA result since the serum for PSA testing is only sampled at the visit and determined at a central laboratory later. After each annual visit prostate biopsy is offered to patients with a PSA of 2.5 ng/ml or more, an abnormal DRE suspicious for prostate cancer or, in some circumstances, a positive family history of prostate cancer.

SABOR participants with 2 or more annual PSA measurements available were stratified into 3 groups according to whether they had undergone prostate biopsy during the followup of 1) no biopsy, 2) 1 or more negative biopsies, or 3) prostate cancer diagnosis. The latter 2 groups were kept distinct. The prostate cancer group included those who had prior negative biopsies but this number was small (6 had 1 prior biopsy, 3 had 2). Only PSA values before prostate cancer diagnosis were included in the analysis. Nonparametric Wilcox tests were used for pairwise comparison of continuous outcomes and covariates among the 3 groups. For categorical summaries the chi-square test was used. All statistical tests were at the $\alpha = 0.05$ (2-sided) level of statistical significance and all statistical analyses were performed using the R statistical package (version 2.6.0, R Foundation for Statistical Computing, 2007).

RESULTS

Of 3,095 men under annual followup in SABOR 2,578 had 2 or more PSA values and were eligible for analysis. Study participants were assigned to 1 of 3 categories of 1) those without prostate biopsy during followup (2,272, 88.1%), 2) those with 1 or more prostate biopsies, all negative for prostate cancer (221, 8.6%), and 3) those with biopsy detected prostate cancer (85, 3.3%, table 1). Participants without prostate biopsy were statistically significantly younger than those who had a prior negative biopsy or those diagnosed with prostate cancer (both $p < 0.0001$), had lower rates of a family history of prostate cancer than participants with a prior negative biopsy or cancer diagnosis (both $p < 0.0001$) and were more ethnically mixed than participants with a prior negative biopsy ($p = 0.01$). There were no statistically significant differences in any of these characteristics between participants with prior negative biopsies and those with a prostate cancer diagnosis. All 3 groups differed significantly from each other in terms of the cumulative number of years of followup (including number of annual PSA measurements available). Cancer cases had the least cumulative followup (maximum of 5 years), followed by the group with no biopsy and the group with 1 or more prior biopsies (all $p < 0.0001$). The last 2 groups had a substantial fraction of subjects followed for 5 years. All 3 groups differed significantly from each other in terms of number of abnormal tests (DRE or PSA 2.5 ng/ml or greater) per person, with the prior negative biopsy and prostate cancer groups having a greater number of abnormal tests (all $p < 0.02$).

Observed fluctuations of the PSA test after an increase of 2.5 ng/ml or greater are shown in table 2. In the majority of incidences an increased PSA was followed by consecutive increased PSAs 1, 2 and even 3 consecutive years later. However, in not insignificant proportions of cases the next consecutive annual PSAs reverted to a status of not increased and remained there. In men who never had a biopsy performed during the study in 23.3% of incidences the next PSA was not increased, in 19.5% the next 2 consecutive PSAs were not increased and in 17.5% the next 3 consecutive PSAs were not increased. Notably the tendency of an increased PSA to revert to not increased at the next visit did not substantially decrease with higher PSA. In men with no biopsy performed, for increased PSA in the ranges of 2.5 to 4.0, 4.0 to 6.0, 6.0 to 10.0 and greater than 10.0 ng/ml, the fractions of time the next annual PSA was not increased were 27.9%, 14.6%, 9.7% and 26.7%, respectively (in 499, 158, 72 and 15 incidences, respectively). Persistence of an increased PSA during the ensuing 1 to 3 years more commonly occurred in

Table 1. *Participant characteristics*

	No Biopsy		1 or More Neg Biopsies		Prostate Ca*	
No. pts	2,272		221		85	
Median pt age at entry (range)	56.0 (28.3, 88.6)		62.0 (33.8, 82.2)		62.8 (45.9, 80.6)	
No. race/ethnicity (%):						
White	1,213	(53.4)	144	(65.2)	50	(58.8)
Black	285	(12.5)	22	(10.0)	13	(15.3)
Hispanic	759	(33.4)	54	(24.4)	22	(25.9)
Other†	15	(0.7)	1	(0.5)	0	(0.0)
No. first degree family members with prostate Ca (%):						
No	1,866	(82.1)	150	(67.9)	54	(63.5)
Yes	406	(17.9)	71	(32.1)	31	(36.5)
No. PSAs during followup (%):						
2	555	(24.4)	17	(7.7)	28	(32.9)
3	469	(20.6)	33	(14.9)	27	(31.8)
4	345	(15.2)	25	(11.3)	22	(25.9)
5	312	(13.7)	44	(19.9)	8	(9.4)
6 or More	591	(26.0)	102	(46.2)	0	(0.0)
No. abnormal DREs during followup (%):						
0 Abnormal	1,895	(83.4)	114	(51.6)	58	(68.2)
1	145	(6.4)	40	(18.1)	15	(17.6)
2 or More	41	(1.8)	36	(16.3)	5	(5.9)
Not performed or result unknown	191	(8.4)	31	(14.0)	7	(8.2)
No. PSAs 2.5 ng/ml or greater during followup (%):						
0	1,806	(79.5)	94	(42.5)	29	(34.1)
1	195	(8.6)	29	(13.1)	18	(21.2)
2	107	(4.7)	17	(7.7)	19	(22.4)
3	67	(2.9)	28	(12.7)	13	(15.3)
4	43	(1.9)	15	(6.8)	4	(4.7)
5	31	(1.4)	10	(4.5)	2	(2.4)
6 or More	23	(1.0)	28	(12.7)	0	(0.0)

* Of patients with prostate cancer 6 had 1 prior negative biopsy and 3 had 2 prior negative biopsies.
† American Indian, Asian or Hawaiian/Pacific Islander.

men with 1 or more negative biopsies performed during study or with an eventual prostate cancer diagnosis ($p \leq 0.03$ for comparisons of these groups to the no biopsy group). Median (range) increased PSAs among the no biopsy, 1 or more negative biopsy and prostate cancer groups were 3.3 (2.5 to 29.8), 4.1 (2.5 to 19.5) and 3.2 (2.5 to 8.9) ng/ml, respectively. PSA decreased by a median of 3.1% at the next annual visit in men with no biopsy, and by a median of 3.6% in those who had 1 or more negative biopsies. In contrast, for men eventually diagnosed with prostate cancer PSA increased by a median of 13.6% at the next annual visit ($p < 0.0002$ for both comparisons to other groups).

Fluctuation of the DRE result from abnormal to normal greatly exceeded that of PSA. Approximately 70% of abnormal DREs were normal the following year (table 3). Even of the 11 instances of an abnormal DRE with 1 subsequent DRE available before a prostate cancer diagnosis the DRE reverted to normal the next year in 8 (72.7%). An abnormal DRE was followed by 2 and 3 consecutive annual normal DREs 69.1% and 68.0% of the time, respectively, in men who had no biopsy performed during followup, and 50.5% and 42.4% of the time, respectively, in men who had 1 or more negative biopsies during followup. Even among men eventually diagnosed with prostate cancer in the majority of instances an abnormal DRE was followed by 2 or 3 consecutive yearly normal DREs (table 3).

Combining PSA and DRE to indicate a positive result if PSA was 2.5 ng/ml or greater, or DRE was abnormal did not improve stability, but rather showed similar but worse characteristics than the PSA 2.5 ng/ml criterion. For example, in the group of men with no biopsy performed in the study, in 234 of 817 (28.6%) instances of a positive combined test the test reverted to negative the next year. In the same group of men in 121 of 505 (24.0%) instances of a positive combined test the next 2 annual tests were negative and in 63 of 299 (21.1%) instances of a positive combined test (where there were at least 3 consecutive annual followup tests) the next 3 annual consecutive tests were all negative.

DISCUSSION

Serum PSA and DRE are the most commonly used tools for prostate cancer screening. Results from this study highlight the flaws of screening approaches that use highly variable tests. Previous studies have evaluated the year-to-year variability of PSA.[7]

Table 2. *PSA results after an increase of 2.5 ng/ml or greater*

	No Biopsy	No. (%) 1 or More Neg Biopsies	Prostate Ca
Next consecutive PSA after increased PSA:*			
Not increased	173 (23.3)	61 (17.3)	6 (8.8)
Increased	571 (76.7)	292 (82.7)	62 (91.2)
Next 2 consecutive PSAs after increased PSA:†			
Both not increased	90 (19.5)	29 (11.1)	0 (0.0)
Both increased	312 (67.5)	194 (74.0)	26 (86.7)
First not increased, second increased	28 (6.1)	14 (5.3)	3 (10.0)
First increased, second not increased	32 (6.9)	25 (9.5)	1 (3.3)
Next 3 consecutive PSAs after increased PSA:‡			
All 3 not increased	50 (17.5)	17 (9.5)	0 (0.0)
All 3 increased	165 (57.9)	117 (65.4)	8 (88.9)
Only 1 increased	35 (12.3)	33 (18.4)	1 (11.1)
Only 2 increased	35 (12.3)	12 (6.7)	0 (0.0)

* Number of increased PSAs (participants) with at least 1 subsequent PSA required to be included in analysis was 744 (368), 353 (124) and 68 (40) for the no biopsy, 1 or more prior biopsy and prostate cancer groups, respectively.
† Number of increased PSAs (participants) with at least 2 subsequent PSAs required to be included in analysis was 462 (246), 262 (106) and 30 (22) for the respective groups.
‡ Number of increased PSAs (participants) with at least 3 subsequent PSAs required to be included in analysis was 285 (168), 179 (82) and 9 (7) for the respective groups.

Eastham et al evaluated 972 participants in the Polyp Prevention trial, all without prostate biopsy and with unknown prostate cancer status, followed for 4 years as part of a study that did not screen for prostate cancer.[7] Outcome measures included an abnormal test based on a PSA greater than 4 ng/ml, a PSA greater than 2.5 ng/ml, a PSA above the age specific cutoff, a PSA from 4 to 10 ng/ml and a free-to-total PSA ratio of less than 0.25 ng/ml, and a PSA velocity greater than 0.75 ng/ml per year. They found that prostate biopsy would have been recommended in 21% of participants with a PSA greater than 4 ng/ml and in 37% with a level higher than 2.5 ng/ml. Among men with an abnormal PSA a high proportion had a normal PSA at 1 or more subsequent visits during 4 years of followup, 44% had a PSA greater than 4 ng/ml and 40% had a PSA greater than 2.5 ng/ml. Based on these findings the authors concluded that an increased PSA should be confirmed several weeks later before proceeding with prostate biopsy. A limitation of their study was the lack of biopsy data on men in whom an increased PSA developed. In contrast, the current study evaluated the roles of PSA as well as DRE in a prospective cohort in which subjects with increased PSA and/or abnormal DRE underwent prostate biopsy. Despite the inherent differences in these patient populations, the findings are strikingly similar. In our study approximately 23% and 40% of men in the no biopsy group had a PSA decrease to less than 2.5 and 4.0 ng/ml, respectively, the next year after the increased PSA, compared to 26% and 30% in the study by Eastham et al.[7] Although the rate of PSA decreasing to less than the cutoff level decreased, with each additional year of followup it remained significant from 23.3% at 1 year to 19.5% at 2 years and 17.5% at 3 years in the no biopsy group. The variability in the DRE results on a yearly basis in this study confirms previous reports of the unreliability and interobserver variability of DRE as a screening tool for prostate cancer.[10–12] Adding DRE to PSA decreased the performance for prostate cancer screening compared to PSA alone while improving it compared to DRE alone.

These data confirm that PSA and DRE, alone or in combination, have significant annual variability, making it difficult to justify their role as the only recommended screening tools for prostate cancer. The unreliability of PSA and DRE testing was seen even in patients diagnosed with prostate cancer, a finding in agreement with observations from prior studies of active surveillance for localized prostate cancer.[13,14]

Our results have implications for the ways PSA and DRE are viewed as screening tools for prostate cancer. Based on these results it is reasonable to repeat PSA and DRE tests before recommending prostate biopsy. The timing of the repeat test would be a flexible decision between clinician and patient. If there was significant concern, it could be per-

Table 3. *DRE results after an abnormal DRE finding*

	No Biopsy	No. (%) 1 or More Neg Biopsies	Prostate Ca
Next DRE after abnormal DRE:*			
Normal	115 (69.7)	76 (67.3)	8 (72.7)
Abnormal	50 (30.3)	37 (32.7)	3 (27.3)
Next 2 DREs after abnormal DRE:†			
Both normal	67 (69.1)	46 (50.5)	5 (62.5)
Both abnormal	12 (12.4)	8 (8.8)	0 (0.0)
First normal, second abnormal	7 (7.2)	12 (13.2)	2 (25.0)
First abnormal, second normal	11 (11.3)	25 (27.5)	1 (12.5)
Next 3 DREs after abnormal DRE:‡			
All 3 normal	34 (68.0)	25 (42.4)	3 (60.0)
All 3 abnormal	2 (4.0)	1 (1.7)	0 (0.0)
1 Abnormal	2 (4.0)	11 (18.6)	1 (20.0)
2 Abnormal	12 (24.0)	22 (37.3)	1 (20.0)

* Number of abnormal DRE findings (participants) with at least 1 subsequent DRE required to be included in analysis was 165 (138), 113 (75) and 11 (10) for the no biopsy, 1 or more prior biopsy and prostate cancer groups, respectively.
† Number of abnormal DRE findings (participants) with at least 2 subsequent DREs required to be included in analysis was 97 (83), 91 (62) and 8 (7) for the 3 respective groups.
‡ Number of abnormal DRE findings (participants) with at least 3 subsequent DREs required to be included in analysis was 50 (46), 59 (39) and 5 (5) for the 3 respective groups.

formed earlier, perhaps within a few weeks. If there was less concern, with less increased PSA levels, a less concerning DRE or an abnormal DRE accompanying a low PSA, it might be reasonable to repeat the test in 6 to 12 months. Performing confirmatory PSA and DRE tests would most likely improve specificity of prostate cancer screening. Conversely, data from the Prostate Cancer Prevention Trial have shown that PSA is a continuous and not a dichotomous marker for prostate cancer detection.[15,16] As such, even if the PSA is repeated and decreases to less than the cutoffs of 2.5 or 4 ng/ml, there is still a risk of prostate cancer and of high grade disease. One approach that would improve the current screening paradigm is to use a risk based, individualized approach to prostate cancer detection via risk calculators and nomograms, which estimate a person's risk of biopsy detectable prostate cancer incorporating PSA and DRE, augmenting their predictive usefulness by including age, race, family history of prostate cancer, history of a prior negative biopsy, the presence of lower urinary tract voiding symptoms, free-to-total PSA ratio, and new biomarkers for prostate cancer as they are discovered and validated.[17,18]

A limitation regarding the results concerning PSA and DRE fluctuation in the group of men eventually diagnosed with prostate cancer is that they only pertain to the period before the prostate cancer diagnosis. In the SABOR screening study followup ceased at diagnosis so there are no data to inform on fluctuation of PSA and DRE after diagnosis. Since many screen detected cancers are likely to have a long latent period and not be immediately treated, it would be of interest to measure expected fluctuation in this circumstance. Long-term followup of a surveillance cohort will be useful for this purpose.

CONCLUSIONS

A single PSA or DRE finding is an unreliable measure for subjecting patients to prostate biopsy. Although more stable than the DRE, occurrences of reversed PSA cut point based decisions to biopsy 1 or more years later are not uncommon, supporting previous suggestions that increased PSA tests be repeated. The inherent deficiencies of single results from screening tools for prostate cancer should be kept in mind while counseling patients concerning prostate cancer detection.

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EDITORIAL COMMENT

Ankerst et al have further demonstrated the limitations of a single PSA value by looking at a serially screened cohort of men in a community based prostate cancer screening study. The principal finding was that among men with a PSA of 2.5 ng/ml or greater not undergoing biopsy, nearly a quarter reverted to a PSA of less than 2.5 ng/ml at the next year's screen. Numbers were similar for men with a history of a negative biopsy where nearly 20% reverted to a normal PSA. While the majority of men experienced a return to abnormal levels, nearly 20% and 10% of men in the unbiopsied and negative biopsy cohorts, respectively, continued to have normal PSA levels for up to 3 years after the increased PSA. These serial screening data confirm previous studies that showed significant annual variation in PSA (reference 7 in article).

While clinicians can take some comfort in knowing that some increased PSA values will decrease to normal levels on followup, this trend may not substantially decrease the risk of harboring prostate cancer. Nearly a quarter of men exhibiting a decreasing PSA pattern in a similar study were subsequently diagnosed with prostate cancer and a substantial number of these men had aggressive cancers.[1] Appropriate vigilance must be maintained even with a decreased PSA.

If a single PSA value must be considered a point on a continuum of risk or as one of a fluctuating set of values, how are clinicians to use PSA to determine a patient's risk of prostate cancer at a given point in time (reference 16 in article)? The authors suggest using PSA as a single component of a comprehensive risk determination, factoring in other variables such as family history, race and previous biopsy data. This is a valid approach but the wide range of predictions and variables used in the various iterations of prostate cancer risk prediction models suggests that this approach needs further refinement. Additionally, this study demonstrates the difficulties in using PSA as a sole tool for prostate cancer screening and indicates that we need to continue our search for better biomarkers of risk.

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